

NASA Contractor Report 3569

NASA-CR-3569 19820021989

Neurochemical Background and Approaches in the Understanding of Motion Sickness

Randall Lee Kohl

CONTRACT NAS9-14880
JULY 1982



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Neurochemical Background and Approaches in the Understanding of Motion Sickness

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Technology Incorporated
Houston, Texas

Prepared for
Lyndon B. Johnson Space Center
under Contract NAS9-14880



National Aeronautics
and Space Administration

**Scientific and Technical
Information Office**

1982

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I. INTRODUCTION

The scientific literature that has been described within this document was originally compiled as appendix material for the Human Use Research Committee Protocol entitled "A Preliminary Evaluation of the Efficacy of Lecithin in the Modulation of Motion Sickness Susceptibility." It was recognized that this literature would be of considerable value to investigators working on the problems of space motion sickness and especially to neurophysiologists and pharmacologists who might need additional understanding of neurochemical mechanisms related to motion sickness or the drugs used to treat and prevent motion sickness. Accordingly, the original text has been reproduced here with minimal edition and supplemented with a Table of Contents and a comprehensive Index. The following pages will present a detailed description of motion sickness, the drugs currently used to treat it, and the metabolic relationships between acetylcholine (ACh) and the anti-motion sickness drugs. Topics will include a pharmacological and neurochemical description of scopolamine and the precursor-product relationship between choline and ACh. The roles of lecithin and its metabolic products in the regulation of the levels of neurotransmitters are characterized as a possible means by which cholinergic neurochemistry can be modulated. A brief discussion of the pharmacodynamics and side effects of lecithin administration in man is presented as well. Summarizing, sufficient information is provided to design and justify experimental research on the central cholinergic system in man.

II. HISTORICAL AND SCIENTIFIC BACKGROUND OF THE RESEARCH

A. MOTION SICKNESS - AN OVERVIEW

The potential incidence of space motion sickness represents an important operational concern during space Shuttle missions. Data from the U.S. and U.S.S.R. manned space programs clearly indicate that without appropriate intervention up to 40% of the astronauts will experience space motion sickness (Graybiel et al, 1974; Homick, 1979; Matsnev, 1980). Various approaches to the problem of treatment and prevention of motion sickness are currently under study. These approaches include: pharmacological, vestibular adaptation training, and biofeedback training procedures. Pharmacological management is presently the most convenient and effective approach to the problem. Orally administered combinations of scopolamine plus amphetamine and promethazine plus ephedrine have been shown to be highly efficacious in preventing motion sickness (Wood and Graybiel, 1968; Graybiel et al, 1975; Graybiel, 1979; Sauerland et al, 1979; Wood, 1979). Such oral medications are relatively short acting and ineffective if administered after symptoms have appeared. The identification of a long term, prophylactic drug for use in space flight is of primary concern. Such a drug must afford good, reliable protection, low incidence of side effects, and be easy to administer.

B. MOTION SICKNESS PHARMACOLOGY - SCOPOLAMINE

Scopolamine is one of the drugs of choice for the treatment and prevention of space motion sickness. The drawbacks to its use include such side effects as central nervous system depression, dry mouth, and loss of visual accommodation. Furthermore, scopolamine is only effective medication for a few hours when it is administered by conventional routes (oral, sublingual, injection). The Neuroscience Laboratory at the Johnson Space Center is currently evaluating the efficacy of transdermally administered scopolamine as an alternative route of drug delivery. A considerable body of literature has accumulated. The transdermal delivery system has been characterized (Shaw et al, 1976; Chandrasekaran and Shaw, 1978; Shaw and Urquhart, 1980) and tests of the ability of the system to modulate motion sickness susceptibility have been performed (Graybiel et al, 1976; Shaw et al, 1977; Graybiel, 1979; McCauley et al, 1979; Price et al, 1979; Graybiel et al, 1981; Laitinen et al, 1981; Wurster et al, 1981). There are indications that this longer acting transdermal therapeutic system (TTS) may be effective in the prevention of motion sickness and cause fewer side effects than oral scopolamine.

Unfortunately, an even larger body of literature indicates that the administration of scopolamine to man can cause impairment of memory (Crow, 1979; Jones et al, 1979; Liljequist and Mattila, 1979; Mewaldt and Ghoneim, 1979; Peterson, 1979; Rassmusson and Dudar, 1979; Rauca et al, 1980), sleep disturbances (Amatruda et al, 1975; Sitaram et al, 1978; Gillin et al, 1979), and prenatal toxicity (Campbell and Ramirez, 1980; Evens and Leopold, 1980). A detailed account of the neurophysiological and neurochemical actions of scopolamine is presented in Section E. The complexity of the effects of scopolamine on the cholinergic nervous system (Section E) underscores the problems inherent in the understanding and use of this drug. The latter sections of this report will indicate the

possible value of manipulation of the cholinergic system through means other than by non-specific receptor blockade. Specifically, modulation of the cholinergic system by control of the availability of choline will be considered in detail (Section F).

C. NEUROCHEMISTRY OF STRESSFUL MOTION

It is reasonable to suggest that cholinergic or histaminergic neurotransmission may be elevated during stressful levels of motion. This suggestion is supported by observations that anticholinergic or anti-histaminergic drugs are effective in the treatment of motion sickness (Wood and Graybiel, 1968; Graybiel et al, 1975; Wood, 1979). Increased turnover of either one or both of these neurotransmitters could be a sign of increased demand for that neurotransmitter, demand for the biosynthetic precursors to these neurotransmitters (choline or histidine), or may instead signal a pathological accumulation of neurotransmitter or its metabolic products.

The administration of either scopolamine or promethazine to cats effectively reduces the spontaneous firing rate of vestibular nuclei. Natural stimulation of the labyrinth normally increases or decreases the firing rate of individual neurons in the vestibular nuclei and scopolamine suppresses these changes in firing rate (Jaju et al, 1970; Jaju and Wang, 1971; Matsuoka et al, 1975). These observations are outwardly consistent with the demonstration that ACh excites the majority (80%) of the cells in the lateral and medial vestibular nuclei in the cat (Kirsten and Sharma, 1976). These findings suggest that sensory information originating in the hair cells of the vestibular apparatus is relayed directly to the vestibular nuclei via cholinergic neurons. Blockade of cholinergic (muscarinic) receptors by scopolamine would hypothetically attenuate the excess transmission that occurs along this central nervous system pathway during stressful motion. This is the simplest model that explains the data presented so far, but unfortunately it appears to be inaccurate. What actually appears to be happening is a complex interaction between cholinergic, noradrenergic and primary sensory afferent inputs in the vestibular nuclei. The interaction is closely related to central nervous system mechanisms of cortical arousal, sensory integration and emotional (visceral) response. These processes are not well understood. An attempt is made in Section E to define the complex interaction described above, but unfortunately "plain english" summaries of the original research findings (Section E) are not often possible or are hypothetical at best.

The neurophysiological picture is further complicated by the existence of an efferent cholinergic loop that modulates the output of the hair cells of the vestibular apparatus (Kirsten and Sharma, 1976; Rossi et al, 1980; Goldberg and Fernandez, 1980). Presumably, these receptors could also be partially blocked by scopolamine even though they tentatively have been identified as nicotinic rather than muscarinic receptors (Kirsten and Sharma, 1976). Muscarinic and nicotinic acetylcholine receptors are two classes of cholinergic receptors that are distinguishable by their preferential interaction with the drugs muscarine and nicotine. (Scopolamine is a muscarinic agent). Theoretically, it should be possible to inhibit the output of peripheral hair cells while simultaneously blocking the afferent excitatory input to the vestibular nuclei by employing two drugs; each one selective for only one class of receptor.

Presently there are few clues as to why both cholinergic and histaminergic antagonists should be effective in the treatment of motion sickness. The next section examines the relationship between these two transmitter systems.

D. ACETYLCHOLINE AND HISTAMINE IN VESTIBULAR SYSTEM FUNCTION

What is the relationship between cholinergic and histaminergic neurotransmission with respect to the possible neurochemical mechanisms underlying stressful motion? Neurophysiologically, both anticholinergics, such as scopolamine and atropine (Jaju et al, 1970; Matsuoka et al, 1975) and antihistaminergics, such as diphenhydramine and dimenhydrinate (Jaju and Wang, 1971), suppress the activity of the cat's vestibular nuclei. These drugs effectively reduce both the spontaneous as well as the electrically or physically induced changes in the firing rate of vestibular neurons. Nowak et al, (1977) has presented experimental evidence favoring the hypothesis that histamine increases cholinergic activity through interaction with H-1 receptors (which may reside on cholinergic neurons). This idea is consistent with reports that antihistamine poisoning is reversed by physostigmine, a drug that inhibits ACh catabolism (Cowen, 1979).

A complementary relationship exists between cholinergic and dopaminergic pathways in the central nervous system that is well characterized. Generally, one system holds another in check. When one system is either over or underactive, as typified by diseases such as Parkinsonism and Huntington's Chorea, the reestablishment of behavioral normalcy is accomplished either by stimulating the deficient transmitter system or by inhibiting the overactive system. Functionally opposed neurochemical mechanisms are natural counterparts of biological control systems. The best understood system is perhaps the autonomic sympathetic-parasympathetic nervous system. Other systems exist that operate at other levels of complexity and subtlety. Section E will examine some neurophysiological pathways that fall into this category. Section F will discuss some neurotransmitter systems that are functionally linked to the individual's state of nutrition. Modification of neurochemical systems by "environmental" chemicals (i.e., food) has been used to beneficially modulate the aberrant transmitter systems in diseases like Parkinsonism and Huntington's Chorea.

If histamine increases cholinergic activity, as suggested above, it should be possible to demonstrate the existence of a functional relationship between histaminergic and dopaminergic neurons. Amphetamine is an effective drug in the treatment of motion sickness (Wood and Graybiel, 1968; Graybiel et al, 1975) and exerts its principal pharmacological action through the stimulation of dopaminergic neurons. Since the administration of histidine was found to antagonize the action of amphetamine (Muley et al, 1979), this provides some evidence that the two transmitter systems are functionally linked, and that histidine may be effective in modulating levels of histamine.

The following section elaborates on the neurotransmitter systems effected by scopolamine.

E. NEUROCHEMISTRY AND PHYSIOLOGY OF MOTION SICKNESS: NEUROPHARMACOLOGY OF SCOPOLAMINE AND AMPHETAMINE

1. Introduction

Considerable evidence has linked scopolamine's central action with modification of cholinergic neurochemistry. Scopolamine is classically regarded as an anticholinergic drug whose principal pharmacological action is blockade of cholinergic receptors. This action accounts for some of its side effects (dry mouth, loss of visual accommodation, and central nervous system depression) and relates to its effects on motion sickness.

The neurochemical actions of scopolamine are more complex than the term "anti-muscarinic" describes. Specifically, the response of different populations of cholinergic neurons to acute doses of scopolamine vary according to the brain region examined; some regions show an increased turnover rate of acetylcholine (ACH) (Wood and Cheney, 1979), others demonstrate increased populations of post-synaptic receptors (Ben-Barak and Dudai, 1980). Although some brain regions reveal elevated concentrations of ACH, total brain ACH levels generally fall. Considerable evidence correlates changes in cholinergic activity with changes in dopaminergic and noradrenergic activity as well (Mason and Fibiger, 1979; Stephens and Herberg, 1979; Engberg and Svensson, 1980). Together these considerations make it difficult to understand the exact mechanism(s) of action of scopolamine in the treatment of motion sickness and suggest that pharmacological manipulation of cholinergic function by other means may prove worthwhile. Manipulation of other neurotransmitter systems, such as the dopaminergic, adrenergic or histaminergic system, is already of therapeutic value as exemplified by the use of promethazine (an antihistaminergic) and amphetamine (a sympathomimetic).

Recently, evidence has accumulated suggesting that activity within some neurotransmitter systems also can be manipulated by regulating the availability of precursors. This literature will be presented later in this appendix (Section F). This section will characterize one way to pharmacologically manipulate the cholinergic system that may prove worthwhile.

The following section is intended to present experimental findings on the neurophysiology and neuroanatomy of pathways in the central nervous system that are involved in the expression of motion sickness, or perhaps more accurately, involved in transmission of sensory information away from the vestibular apparatus. The neurophysiological changes elicited by antimotion sickness drugs are reviewed also.

2. Neurophysiology and Neuroanatomy

The initial neuronal events that follow a motion stimulus are fairly well understood (see Figure 1). Stimulation of the hair cells in the vestibular apparatus of the inner ear by the motion stimulus results in increased or decreased output from the hair cell depending on the direction of motion and the specific hair cell considered (Goldberg

Interactions of the Vestibular Nuclei with the Vestibular Apparatus and Brain Stem Nuclei

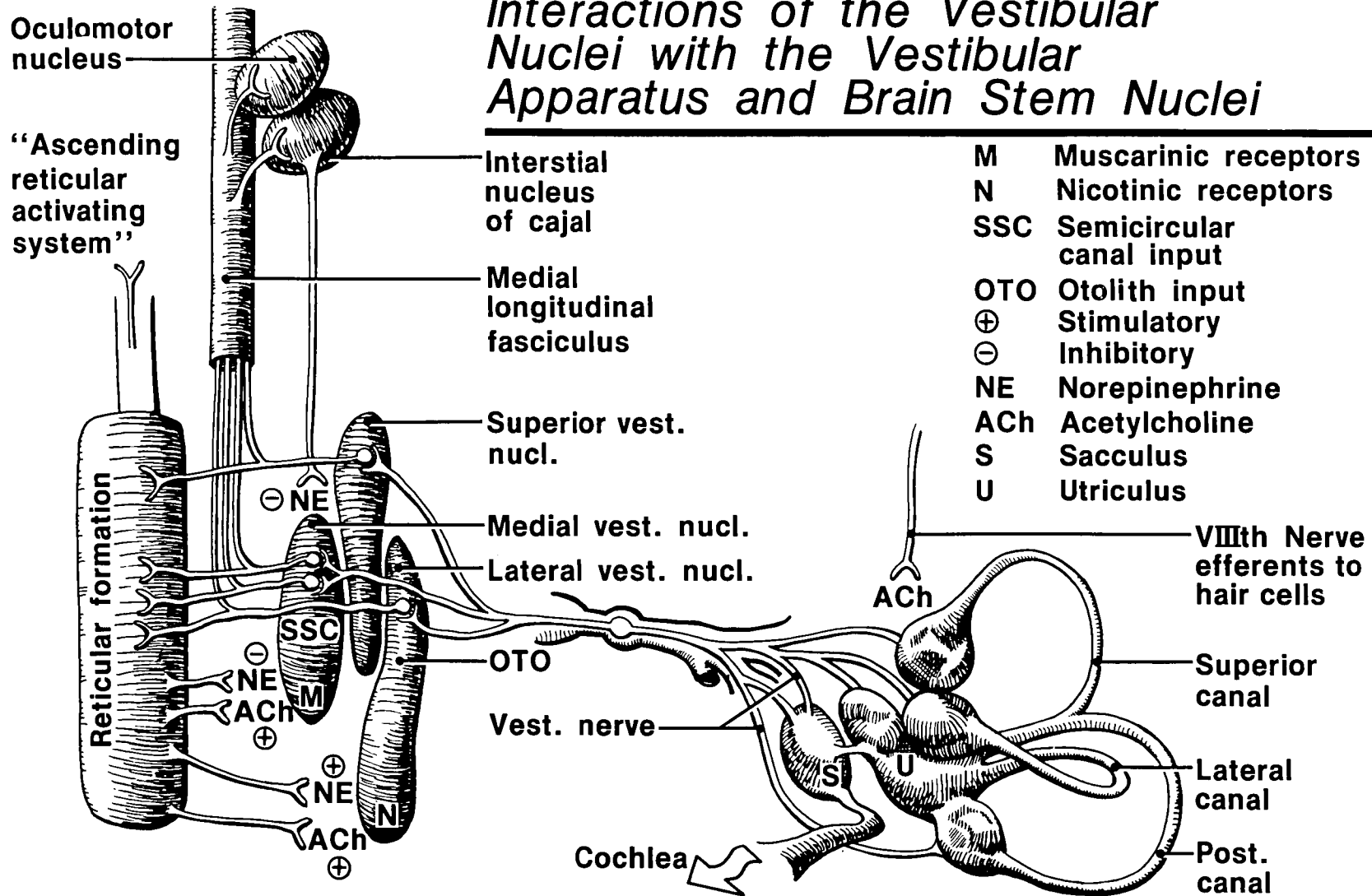


Figure 1

and Fernandez, 1971; Budelmann, 1979). This arrangement allows fine discrimination of direction and magnitude of motion. The neurotransmitter substance that is released by the hair cells to stimulate the primary sensory afferents is unknown. There is evidence against ACh or norepinephrine being that transmitter (Matsuoka and Domino, 1975; Drescher, 1981) and some speculation and evidence that GABA, glutamate or Met-enkephalin might be involved (Flock and Lam, 1974; Meza et al, 1981; Bobbin et al, 1981; Drescher, 1981; Hoffman et al, 1981; Wenthold et al, 1981).

Afferent output from the vestibular apparatus is relayed to the vestibular nuclei in the brain stem. The neurotransmitter released onto these nuclei by the primary sensory afferents is also unknown. Ample histochemical and pharmacological evidence suggests that ACh functions as an afferent neurotransmitter in the vestibular nuclei. Because of the multiplicity of projections to the vestibular nuclei, and especially the abundance of non-labyrinthine synaptic connections, the association of the primary afferent pathway or any pathway with a specific neurotransmitter is difficult. According to the work of Kirsten and Sharma (1976), ACh excites 80% and 86% of the neurons located in the medial and lateral vestibular nuclei of cats, respectively.

The medial vestibular nucleus in the cat receives projections from the semicircular canals and descending afferents from the nucleus of Cajal; a pathway involved in the modulation of head and eye movements (Markham, 1972). However, it is unlikely that the input from the semicircular canals is cholinergic (Kirsten and Schoener, 1973; Matsuoka and Domino, 1975). The afferent input from the nucleus of Cajal is probably noradrenergic. Norepinephrine and amphetamine inhibit 75% of the cells in the medial vestibular nucleus. Phentolamine, an α -blocker, does not block the inhibitory response to norepinephrine. This suggests that the nucleus processes β -adrenergic receptors similar to those possessed by the hippocampus (Segal and Bloom, 1974). Interestingly, 68% of the cells inhibited by norepinephrine and amphetamine were excited by ACh (Kirsten and Sharma, 1976).

The lateral vestibular nucleus in the cat receives afferent input from the otolith organs (Schor, 1974). Norepinephrine and amphetamine excite 63% of the cells in the lateral vestibular nucleus of the cat through interaction with α -receptors. This excitatory input is blocked by classical α -blockers such as phentolamine. All of the cells excited by norepinephrine and amphetamine are also excited by ACh (Kirsten and Sharma, 1976).

Application of a motion stimulus to cats has revealed that 35% of the neurons in the medial and lateral vestibular nucleus are sensitive to motion. The great majority (79%) of these motion responsive cells are located in the medial vestibular nucleus. Autoradiographic localization of muscarinic cholinergic receptors in rat has indicated that the medial vestibular nucleus contains many muscarinic receptors whereas the other vestibular nuclei contain few receptors (Lewis et al, 1980). The medial vestibular nucleus receives afferents from the

semicircular canals. The lateral vestibular nucleus responds to reticular formation stimulation. This excitatory response is primarily nicotinic and can be blocked by the nicotinic antagonist, mecamylamine, but not by the peripherally acting antagonist, methadonium. L-Dopa or amphetamine enhances the excitation of these neurons in the cat by stimulation of the reticular formation (Matsuoka and Domino, 1975). Previous studies have indicated that the neural output or firing rate of the vestibular afferents, vestibular nuclei and vestibular related cerebellum in the dogfish is proportional to the degree of motion stimulation (Montgomery, 1980). The spontaneous discharge rate of the cat's lateral vestibular nucleus (19.8 ± 0.9 Hz) is not influenced by a spinal cut (18.0 ± 1.6 Hz) but is decisively lowered by scopolamine (Matsuoka *et al.*, 1975). Despite the involvement of ACh in the neurochemistry of the vestibular nuclei, very little choline acetyltransferase is found. This contrasts strongly with the cranial motor nuclei which are very high in choline acetyltransferase (Kobayashi *et al.*, 1975). Further discussion of the role of choline acetyltransferase in the biosynthesis of ACh will be deferred to section F (Choline-ACh Relationships).

It is possible to eliminate norepinephrine as the primary afferent neurotransmitter in the vestibular nuclei because there is no correlation between the sensitivity of the nuclei to motion and the effect of iontophoretically applied norepinephrine or amphetamine. Secondly, depletion of brain catecholamines by reserpine does not block synaptic transmission and there is no decrease in the number of cells responding to acceleratory motion. Lastly, ACh does not mimic the response to norepinephrine or amphetamine.

It is possible to eliminate ACh as the primary afferent transmitter because anticholinergic agents are without effect on the field potentials evoked by VIIIth nerve stimulation. Hence, the sites at which antimuscarinic agents act to depress the activity of vestibular nuclei must be other than those in the afferent pathway leading directly from the labyrinth to second order vestibular neurons. The well-documented synaptic complexities present within the vestibular nuclei, especially the abundance of non-labyrinth synaptic connections, suggests a complex neuronal interaction. The many observations of the influence of the reticular formation on vestibular activity provides evidence that the inhibition of vestibular units by scopolamine is the result of a modified input from the reticular formation (Kirsten and Schoener, 1973). The possible roles of the reticular formation and other pathways that are influenced by scopolamine and amphetamine will be considered later in this section.

3. Labyrinth Efferents

The efferent innervation of the hair cells in the lateral line organs of lower vertebrates (Russell and Roberts, 1974; Flock and Russell, 1976) in the mammalian cochlea (Wiederhold, 1970; Bobbin and Konishi, 1974) and in the frog (Gribenski and Caston, 1976) is cholinergic and inhibits afferent outflow from the sense organ. This cholinergic effect is blocked by curare and partially blocked by atropine. An increase in the conductance of chloride channels residing on the

sensory hair cells is the proposed mechanism by which ACh inhibits afferent outflow (Rossi et al, 1980). This change in conductance which is measured on the hair cell as an inhibitory postsynaptic potential change means that there is a drop in the impedance across the hair cell's membrane. It follows, therefore, that small changes in receptor currents in response to sensory stimulation would generate lower transmembrane voltage changes and a lower probability of primary sensory afferent discharge. These authors have speculated that efferent control of the semicircular canal can extend the dynamics of this sensory organ to a wider range of stimulus intensities. It has been demonstrated that a single efferent neuron innervates many hair cells, irrespective of their directional sensitivity, so that sensory activity can be controlled peripherally at the receptor level. It has been estimated that the activity of some 10,000 to 20,000 vestibular afferents (Gacek and Rasmussen, 1961) is modulated by only 400 to 600 efferent neurons (Gacek et al, 1965; Gacek and Lyon, 1974; Warr, 1975; Goldberg and Fernandez, 1980).

Goldberg and Fernandez (1980) have presented convincing evidence that efferent modulation of the hair cells in the squirrel monkey (Saimiri sciureus) is excitatory rather than inhibitory. The main efferent group is a circumscribed column of cells interposed between the abducens and the superior vestibular nuclei which they designated group e. Because the vestibular afferents have a potential dynamic range of 0 to 400 spikes per second but usually operate in the lower end of the range (Goldberg and Fernandez, 1971; Fernandez and Goldberg, 1976), these authors have speculated that efferent excitation extends the dynamic response range of the sensory system to expected motion. If the resting discharge rate of the system was not elevated, large accelerations in one direction would cause the output of some sensory elements to drop to zero with a consequent loss in linear response. This is because the system is operating under normal conditions of postural maintenance at a low level of resting output and because motion in a given direction affects the direction of change in discharge rate differently depending on the particular hair cell examined (Goldberg and Fernandez, 1971; Budelmann, 1979). According to these authors, the extension of the dynamic range through efferent stimulation would not only assure a linear response to sensory stimulation of those cells whose output is decreased by a particular direction of motion, but also might increase the drive to the vestibulo-ocular reflex, for example, so that a readiness to respond to anticipated angular accelerations is maintained. These rationalizations are consistent with the observations that little topographic specificity exists between individual efferents and the afferents whose discharge they modify.

A biological explanation for the presence of excitatory efferents in the squirrel monkey and most likely in the cat as well (see Goldberg and Fernandez, 1980) is not at all difficult in light of the foregoing and the fact that inhibition of lateral line output in a swimming invertebrate would be the appropriate response to prevent overstimulation of receptors designed to detect local movements of water. Neurophysiologically, it has been proposed that an efferent action on the target cell, rather than on the hair cell itself, would facilitate

discharge of primary sensory afferents. Further investigation of the mechanisms are warranted.

Experimentation which entails a precursor load strategy, may prove to be of therapeutic value in the prevention of motion sickness because it makes available to the nicotinic efferent nerve ending a greater supply of the transmitter, ACh. There is evidence that choline administration not only elevates the amount of stored ACh at the presynaptic nicotinic nerve terminal, but also increases the number of nicotinic receptors that are responsive to this ACh on the postsynaptic membrane (Morley et al, 1977).

4. Scopolamine and Amphetamine: Effects on Cortex

Amphetamine is a anti-motion sickness drug that has been proven effective in the prophylactic treatment of motion sickness. Combinations of scopolamine and amphetamine, or promethazine and amphetamine are more effective than either scopolamine, promethazine or amphetamine alone (Wood and Graybiel, 1972). Furthermore, reversal of the central nervous system depression that often follows the use of scopolamine or promethazine is regarded as an additional advantage of amphetamine. It may be possible to ascertain which neurophysiological effects comprise the anti-motion sickness actions of these drugs by comparison of the neurophysiological effects of each drug. The following paragraphs will present detailed accounts of the neurophysiological actions of amphetamine and scopolamine. Very little data is available on the actions of promethazine.

Scopolamine increases the turnover rate and output of ACh in the cerebral cortex and synchronizes the EEG in both the rat and cat (Nistri et al, 1974; Mantovani et al, 1980). Amphetamine also increases the turnover rate and output of ACh in the cortex but causes activation of EEG (Nistri et al, 1972, Schmidt, 1976). Both drugs reduce absolute concentrations of ACh in cortex (Schmidt, 1976; Wood and Cheney, 1979). Changes in cortical neurochemistry can be related to man's state of consciousness because the cerebral cortex is recognized as the seat of consciousness. Levels of conscious awareness can be roughly correlated with the degree of cortical EEG desynchronization (or activation). Further attention will be given to the neurophysiological mechanisms that control cortical activity because of the need to control the CNS depression that often follows anti-motion sickness medication.

Stimulation of the midbrain ascending reticular formation causes desynchronization of the EEG and increases ACh output in the cortex several fold. The course and distribution of acetylcholinesterase - containing fibers in the forebrain suggests that they form the anatomical basis of the ascending reticular activating system which is responsible for electrocortical arousal. This system is not wholly responsible for arousal of the animal since blockade of cholinergic terminals at the cortical level (by scopolamine) is not sufficient to maintain a synchronized EEG. Noncholinergic corticopetal fibers are also derived from the reticular thalamic nucleus. Evidence suggests that electrocortical arousal is mainly a cholinergic phenomenon,

mediated by the corticopetal radiations of the ascending cholinergic reticular system. Behavioral arousal, on the other hand, may involve subcortical pathways, not all of which are cholinergic (Shute and Lewis, 1967). There is evidence that monoamines released by amphetamine have an inhibitory effect on synaptic transmission in the cortex. This action opposes that of the cholinergic system but its prominence is not nearly as great as that of the cholinergic system. Interpretation of the foregoing conflict in the context of the neurological consequences of administration of scopolamine and amphetamine is not problematical if one invokes the following assumptions: First of all, the CNS depression that follows scopolamine is directly related to diminished "transmission" at the cortical level. Because scopolamine is blocking the receptors, and thus "transmission", the compensatory rise in ACh output may be regarded as an attempt by the system to reestablish equilibrium; that is, to overcome the blockade. Secondly, the effects of amphetamine on ACh release is probably more closely related to its effects on subcortical systems such as the limbic system (discussed below) or the brain stem reticular activating system.

5. The Limbic System

The limbic system is a subcortical system that also is profoundly affected by both scopolamine and amphetamine (Figure 2). The limbic system includes the hippocampus, the amygdaloid nucleus, the hypothalamus (especially the mammillary bodies), and the anterior nucleus of the thalamus. The fornix, mammillothalamic tract, and stria terminalis are the fiber bundles of the limbic system. It is known as the "visceral brain" because it is functionally associated with emotional aspects of behavior related to survival of the individual and the species, together with "visceral responses" accompanying these emotions, and the brain mechanism for memory. The visceral responses to activity within the limbic system are mediated mainly through the hypothalamus and include changes in respiration, gastrointestinal movements and secretion, piloerection, and pupillary dilation. Understanding of neurophysiological regulation of visceral functions is primary to elucidation of the neural components of motion sickness and the neuropharmacological bases of anti-motion sickness drug therapy.

Electrocortical arousal by reticular stimulation of hippocampectomized cats is difficult and, unlike the arousal obtained in normal animals, lasts only for the duration of the stimulus. It is likely that these hippocampal effects are achieved by influences acting on some part of the brain external to the hippocampus, rather than as an intrinsic property of the hippocampus itself. A major output from the hippocampus passes directly through a relay in the mammillary body to elements of the cholinergic limbic system which connect directly with medial cortex or, through links with the ascending cholinergic reticular system, with the lateral cortex of the cerebral hemispheres (Lewis and Shute, 1967). Thus, the limbic system may be critical to maintaining alertness.

Relationship of Ascending Reticular, Limbic, Hypothalamic and Cortical Systems

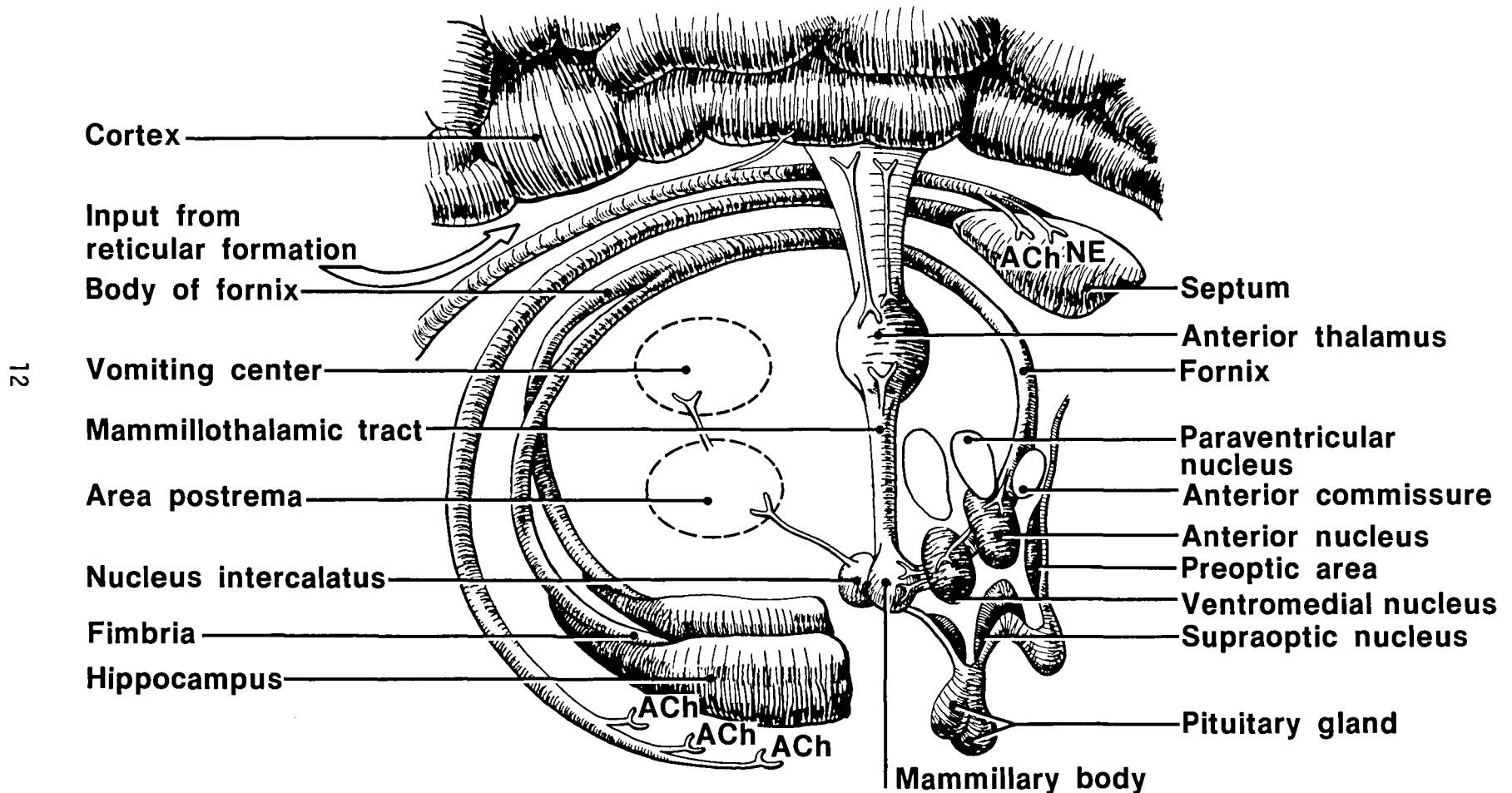


Figure 2

Although superficially both nicotine and muscarinic agonists induce an alert EEG, their effects differ in several important aspects. Nicotinic arousal of the EEG may depend on the intactness of the reticular formation, as compared with the more diffuse arousal of the EEG caused by muscarinic agonists (Domino et al, 1967).

6. Scopolamine and Amphetamine: Effects on Limbic Structures

Scopolamine increases ACh outflow in the cerebral cortex by an action on subcortical, limbic structures (Figure 2). Cortical release of ACh by scopolamine is blocked by lesions in the septum, fornix, or fimbria of cats and rats (Nistri et al, 1972, Mulas et al, 1974, Mantovani et al, 1980) and by cortical undercutting (Nistri et al, 1972). Lesions of the septal nuclei destroy the major cholinergic cell bodies that send afferents to the hippocampal limbic structures. Lesions of the fornix (and fimbria) block the non-cholinergic output of the hippocampus. It is believed that this non-cholinergic outflow eventually reaches the ascending cholinergic reticular system which projects to the cortex. It is reasonable to suggest that this interaction of the limbic system with the ascending reticular system is essential to the cats' ability to maintain arousal. If such a mechanism does exist, it most likely involves a pathway originating from the hippocampus that travels with the fibers of the fornix to the mammillary bodies in the hypothalamus. The major efferent connections of the mammillary bodies are via the mammillothalamic tract to the anterior thalamic nuclei. The nuclei of the anterior thalamus are non-specific nuclei that have extensive reciprocal connections with the association cortex (cingulate gyrus) (Mountcastle and Poggio, 1968; Bard, 1968, Mountcastle, 1968; Barr, 1974). Lesions of septum, fornix, fimbria and cortical undercutting may all impair the role that this thalamic radiation plays in maintaining arousal.

Amphetamine increases ACh outflow in the cerebral cortex by an action that also is dependent on an intact limbic system since septal lesions prevent the increase (Nistri et al, 1972). Amphetamine induces short term increases in level of ACh in the striatum and cerebellum and simultaneous decreases in the level of ACh in cortex and hippocampus (Schmidt, 1976). This is consistent with amphetamine-induced changes in the turnover of ACh. Although amphetamine can activate EEG by stimulation of the midbrain reticular formation, an intact reticular formation is not necessary for the drug effect. Ablation of the septum, which prevents amphetamine elicited release of ACh in the cortex, does not block the EEG activation. Apparently, at least two mechanisms exist for EEG activation by amphetamine.

Many collateral pathways are derived from the pathways linking hippocampal efferents with the anterior thalamus. Fibers that leave the fornix and terminate in the anterior hypothalamic nuclei and the nucleus intercalatus in the mammillary bodies are of particular interest to the study of motion sickness. The anterior hypothalamic nuclei exert a major influence on the visceral organs. The predominantly parasympathetic outflow from this region will increase sweating, vasodilation, salivation, and peristalsis of the gastrointestinal tract while decreasing heart rate and blood pressure. All of these

peripheral effects can and do occur in motion sickness. The nucleus intercalatus sends efferent fibers to the area postrema which in turn innervates the "vomiting center" (Reason and Brand, 1975; Vigier and Rouviere, 1979). The apparent blockade of the septohippocampal pathway by scopolamine could both diminish the peripheral symptoms of motion sickness and block neuronal pathways to the vomiting center.

Stimulation of the (mesencephalic) reticular formation increases ACh release from the hippocampus. Section of both fornices does not alter spontaneous release of ACh from the hippocampus, but does prevent release mediated by the reticular formation. The administration of amphetamine acts exactly like stimulation of the reticular formation; the increased release of ACh is also prevented by section of the fornices. Scopolamine also increases ACh release from the hippocampus. This release occurs following topical applications of the drug and occurs with or without cut fornices.

Wood and Cheney (1979) have attempted to distinguish whether a neuronal feedback loop or a presynaptic muscarinic receptor mechanism could be invoked to explain the actions of scopolamine on the turnover rate of ACh in the septo-hippocampal cholinergic pathway. They concluded that the cholinergic systems of the hippocampus and thalamus possess self-regulating feedback mechanisms that are markedly perturbed by muscarinic receptor blockers. The perturbation is expressed by a two-fold elevation in the turnover of ACh in the hippocampus. In support of this conclusion, they described experimentation that (1) ruled out the presence of presynaptic muscarinic binding sites in the hippocampus, (2) negated any role of inhibitory cholinergic neurons in the septum, and (3) demonstrated that the blockade of the stimulatory noradrenergic input to the septum does not influence the increased turnover rate of ACh in the hippocampus that follows scopolamine administration. The authors suggested that axonal collaterals of the cholinergic septal neurons may activate noncholinergic inhibitory interneurons which in turn act on the cell bodies.

7. Conclusions

The influence of anti-motion sickness drugs on the vestibular nuclei is well documented. It appears that neither ACh nor norepinephrine are directly involved in primary sensory transmission at the end organ (the hair cell) or at the vestibular nuclei, but instead play prominent roles in modulating the activity of vestibular nuclei. The involvement of the cholinergic ascending reticular activating system and the limbic system with higher nervous system functions is apparent as is the relationship of these pathways to the expression of both the symptoms of motion sickness and the side effects of the anti-motion sickness drugs. Because of the complexity of the central cholinergic system and the systems with which it interacts, it is not only difficult to design a new therapeutic approach to manage motion sickness, but it is even perplexing to define the mechanism of action of the proven anti-motion sickness drugs.

The authors want to stress the possibility that the "medial" vestibular nucleus may be a site of particular importance in the action of

the known anti-motion sickness drugs and, consequently, the medial nucleus may play an essential role in the normal neurophysiological mechanisms underlying motion sickness. The medial vestibular nucleus is distinguished from the remaining nuclei on the basis of its afferent input, its response to ACh, norepinephrine and anti-motion sickness drugs (see Figure 1). The medial vestibular nucleus receives its input from the semicircular canals and from the interstitial nucleus of Cajal (Markham, 1972). The latter input is presumably noradrenergic and concerns the modulation of eye and head movements. The medial vestibular nucleus is stimulated by ACh and inhibited by NE, whereas the lateral vestibular nucleus is stimulated by both transmitters (Kirsten and Sharma, 1976). "Muscarinic" cholinergic receptors are sparse on the lateral vestibular nucleus but abundant on the medial nucleus (Lewis et al. 1980). The equal effectiveness of scopolamine (0.6 mg) and amphetamine (20 mg) in the prevention of motion sickness favors assessment of the medial vestibular nucleus as an important relay station in the expression of motion sickness. The fact that 79% of the vestibular neurons that are responsive to motion stimuli are located in the medial vestibular nucleus further supports this contention (Kirsten and Sharma, 1976).

The common denominator throughout this section has been ACh; it modulates the activity of peripheral hair cells, central vestibular nuclei, the parasympathetic autonomic nervous system and other central mechanisms as well. The problem with anticholinergic motion sickness drugs is that they are nonspecific muscarinic blockers. An alternative pharmacological intervention has been suggested that is based on the administration of normal dietary constituents. Lecithin or choline will modulate cholinergic activity through elevation of the circulating levels of choline; the immediate biochemical precursor of ACh. The influence of choline on cholinergic function will be discussed in the next section. Although the effects of choline are distinctly different from those of scopolamine, selectivity for the cholinergic system is still retained. There is no reason to assume that a specific blockade of (a) muscarinic receptor(s) is key or essential in the "anti-motion sickness" effects of scopolamine.

F. THE CHOLINE-ACETYLCHOLINE RELATIONSHIP

1. Introduction

Choline and phosphatidylcholine (lecithin) are recognized as effective modulators of cholinergic neurochemistry (Cohen and Wurtman, 1976; Consolo et al., 1979). Both the levels of ACh in brain and the functional activity of cholinergic neurons (Ulus and Wurtman, 1976; Ulus et al., 1977; Haubrich and Pflueger, 1979) are reported to rise shortly after a choline or lecithin meal. The action of choline on this neurotransmitter system is well established in terms of fundamental enzyme kinetics (White and Wu, 1973, Marchbanks and Wonnacott, 1979; Fernstrom and Wurtman, 1979), behavioral end points (Wecker and Schmidt, 1979), and in clinical disorders of cholinergic function such as tardive dyskinesia and Huntington's Chorea (Barbeau, 1978; Kolata, 1979; Zeisel et al., 1980a).

Control of the functional activity of a particular type of neuron or at least regulation of the size of individual neurotransmitter pools by the physiological precursor substance is not a new idea, nor is it restricted to only one neurotransmitter system (Fernstrom and Wurtman, 1974; Smith *et al.*, 1977; Wurtman and Fernstrom, 1976; Growdon and Wurtman, 1978). Neurons that use ACh, norepinephrine and 5-hydroxytryptamine as their chemical neurotransmitter are known to be responsive to circulating levels of their respective precursors, namely, choline, tyrosine (Gibson and Wurtman, 1978) and tryptophan (Fernstrom and Wurtman, 1971). The levels of other important intermediates in brain, namely, histamine and S-adenosylmethionine, also appear to be strongly influenced by the availability of their immediate precursors, histidine and methionine (Taylor and Snyder, 1972; Rubin *et al.*, 1974; Pollard *et al.*, 1974)). What appears to be emerging in current thought is the concept that the brain is not an organ that is metabolically isolated from the rest of the body by a blood-brain-barrier, but rather, responds dynamically to both peripheral chemical and sensory inputs (Fernstrom and Wurtman, 1974). It is believed that this responsiveness is accomplished through neurochemical sensing mechanisms such as those embodied by neuronal precursor-product relationships as described in this section.

2. Overview of Factors Which Control Synthesis of Acetylcholine at the Nerve Terminal

a. Choline Acetyltransferase and Acetylcholine Synthesis

Choline is the physiological precursor of ACh whose acetylation is catalyzed by the enzyme choline acetyltransferase (CAT) using acetyl-CoA as the acetate donor. The enzyme is normally very unsaturated with its substrate choline. Its K_m for choline is about 400 μ M, whereas brain choline levels vary between 35 and 100 μ M (Cohen and Wurtman, 1976). Manipulations that elevate brain choline will enhance the saturation of CAT and cause more ACh to be synthesized.

b. Choline and Acetylcholine Synthesis

Choline given intravenously or via the diet sequentially raises brain choline and then ACh levels (review: Haubrich, 1979). Insignificant amounts of choline can be synthesized *de novo* in the brain (Jenden, 1979; Zeisel *et al.*, 1979). The brain derives its choline from the blood in both free and lipid bound (e.g., lecithin) form.

There is some evidence that amphetamine may alter lecithin metabolism so as to favor the formation of free choline. This is because the incorporation of (14 C) choline into phosphatidylcholine was inhibited by amphetamine, whereas phospholipase C (which initiates conversion of lecithin into choline) appeared unaffected (Hitzemann and Loh, 1973). Although chronic amphetamine administration increased choline acetyltransferase in brain (Ho and Gershon, 1972), this observation should not be regarded as a direct effect of amphetamine on the cholinergic system. It is

more likely that the rise in choline acetyltransferase is a response to elevated noradrenergic activity instead.

c. Choline Intake and Acetylcholine Synthesis

ACh that is released from the nerve terminal can not be taken up by the nerve terminal or any other cell until it is metabolically broken down into choline and acetate. Abundant supplies of acetylcholinesterase are present in the region of the nerve terminal to effect this cleavage. A high affinity uptake mechanism exists for the transport of choline into the presynaptic terminal. Cholinergic neurons appear to be the only cells which possess the high affinity uptake system. When choline is taken up by the nerve, it is used for the synthesis of ACh. The degree to which this uptake is coupled to the uptake process is in dispute (50-80% is acetylated). There is ample and convincing evidence which demonstrates that the high affinity choline transport system is responsible for a significant portion of ACh synthesized in brain, in vivo (review: Simon et al, 1976; Fisher and Hanin, 1980).

d. Choline Uptake and the Functional Activity of Cholinergic Neurons

The uptake of choline by the nerve terminal is proportional to the turnover rate of ACh (Kuhar and Murrin, 1978). Drugs which are effective in altering the turnover rate of ACh, such as scopolamine, atropine, physostigmine and Δ^9 -tetrahydrocannabinol, also cause corresponding changes in choline uptake. The neurochemical mechanism underlying this effect is not well understood. There is some evidence that intracellular stores of ACh regulate the functional activity of the choline transport site through occupation of the cytosolic binding sites on the carrier. The competition for choline binding sites is diminished upon release of intracellular stores of ACh, such as would follow nerve stimulation (Marchbanks and Wonnacott, 1979). When mice are treated with atropine 30 minutes before sacrifice, a dose-dependent increase in high-affinity choline uptake can be measured in isolated crude synaptosomal preparations that is particularly pronounced in hippocampus and cortex but not in striatum (Eckernas et al, 1980). If intracellular levels of ACh participate in the regulation of choline uptake, it would follow that choline is accumulated with some degree of selectivity by those neurons actively involved in transmission. Thus, the pharmacological effects of the administration of choline (or lecithin) would differ from that of scopolamine in an important respect; that is, scopolamine would nonspecifically block all muscarinic receptors, whereas, high circulating levels of choline would act as a buffer to the functional activity of the cholinergic system. Although a strong argument can be made for the association of the side effects of scopolamine with its nonspecific blockade of receptors, no such argument exists for the correlation of high choline availability with a therapeutic benefit of choline in motion sickness. Fortunately, there is no strict correlation between muscarinic receptor blockade and an anti-motion sickness effect since amphetamine (20 mg), is as effective as scopolamine (0.6 mg) (Wood and Graybiel, 1968, 1972).

3. Modulation of the Central Effects of Antimuscarinic Drugs by Choline

A high dose of atropine ordinarily leads to the depletion of ACh in cortex and hippocampus, an increased turnover of ACh and accelerated uptake of choline. If choline is administered one hour before atropine, these changes do not occur (Wecker et al, 1978). Although the acute administration of choline reduces the effects of atropine, chronic choline loading renders central muscarinic receptors more responsive to two effects of atropine, viz., ACh depletion and locomotor hyperactivity. These effects could result from altered sensitivity or number of receptors (Wecker and Schmidt, 1979).

4. Conclusions

The difficulties encountered in attributing a specific set of pharmacological actions to the therapeutic benefit of scopolamine in motion sickness are a consequence of its many neurochemical actions. If depletion of ACh at the peripheral inhibitory synapse compromises regulation of the sensory output of the labyrinth, then an elevated circulating supply of choline may be of therapeutic value. If alteration of the dynamics of cholinergic activity in the cortex and hippocampus is responsible for the side effects of scopolamine, then choline might effectively diminish these side effects as well. It is entirely possible that the greatest benefit might eventually derive from the simultaneous administration of both choline and scopolamine. The experimental testing of this hypothesis will necessarily have to follow the determination of the effects of choline alone and the subsequent reassessment of those neurochemical actions of scopolamine which are meaningful to the prophylactic treatment of motion sickness.

G. NEUROCHEMICAL AND NEUROPHARMACOLOGICAL CONTROL OF PITUITARY HORMONES

1. Relationship of Pituitary Hormones and Motion Sickness

Eversmann et al (1978) have reported that the stress of motion sickness in man leads to increased levels of growth hormone, cortisol, prolactin and antidiuretic hormone (ADH) in plasma. Plasma levels of thyrotropic hormone (TSH) were decreased while the urinary excretion of triiodothyroxine and thyroxine increased (Habermann et al, 1978). These authors concluded that ADH secretion was the most sensitive indicator of motion sickness and that endocrinological factors in general, could be used to evaluate susceptibility to motion sickness. However, the increase in hormone secretion correlated well with only the number of stressful head movements and the increasing degree of motion sickness within individual subjects.

Amphetamine influences secretion of TSH and prolactin from the pituitary (Lu and Meites, 1971; Ravitz and Moore, 1977; Spindel et al, 1978). Since this action of amphetamine is augmented by treatments that accelerate dopamine synthesis (Clemmens and Fuller, 1979), the drug probably exerts its influence on pituitary hormones by releasing dopamine (Watkins et al, 1979). It has been fairly well established that dopamine is the prolactin inhibitory factor (Caron et al, 1978; Weiner and Ganong, 1978).

TSH, prolactin and growth hormone are three anterior pituitary hormones whose modulation by cAMP, brain neurotransmitters, hypothalamic releasing factors and peripheral stress is well established (Spindel et al, 1980). Growth hormone is released in humans by stress (Martin et al, 1977) and by ACh in bovine pituitary slices (Young et al, 1979). Treatments which increase 5-hydroxytryptamine synthesis in brain, such as administration of the precursor amino acid, tryptophan, will enhance growth hormone secretion in the rat (Arnold and Fernstrom, 1981). The effects of tryptophan on the release of growth hormone in man is not as pronounced as that in the rat but is similar (Muller et al, 1974; Woolf and Lee, 1977, Glass et al, 1979).

Cortisol secretion is increased by the systemic and intrahypothalamic administration of cholinomimetic drugs, and decreased by anticholinergic agents (Endroczi et al, 1963; Krieger et al, 1968; Cozanitis, 1974; Hillhouse et al, 1975). The secretion of growth hormone in vivo may be influenced by cholinergic agents (Blackard and Waddell, 1969; Salvadorini et al, 1975, Mendelson et al, 1978). Prolactin secretion is usually inhibited by cholinergic agonists under circumstances of active prolactin release (Blake and Sawyer, 1972; Grandison et al, 1974; Lawson and Gala, 1975). Davis and Davis (1980) have reported that the administration of methscopolamine and physostigmine to man did not affect secretion of cortisol, growth hormone or prolactin. However, they observed that in those subjects who became nauseated or vomited (some of whom received larger doses of physostigmine), levels of cortisol, growth hormone and prolactin were markedly elevated. These results confirm earlier findings with physostigmine (Sachar et al, 1977; Carroll, 1978) in which nausea, pallor, vertigo and increased sweating were all accompanied by large elevations of cortisol, prolactin and growth hormone in plasma. When physostigmine is given by slow infusion it is possible to obtain these hormonal responses without nausea (Carroll, 1978).

Muscarinic receptors have been identified in the anterior pituitary of both rat and sheep (Burt and Taylor, 1980; Schaeffer and Hsueh, 1980). However, only low levels of acetylcholinesterase have been found in bovine anterior pituitary, approximately 2 and 8 percent of whole brain levels, respectively (LaBella and Shin, 1968). These muscarinic receptors are responsive to cholinergic drugs. Using organ-cultured anterior pituitary, it has been shown that ACh agonists such as carbachol and pilocarpine stimulate mitotic activity, whereas, scopolamine and atropine inhibit mitotic activity (Pawlikowski et al, 1978). Since there is no established cholinergic or other innervation to the anterior pituitary, the presence there of typical muscarinic receptors suggests that ACh reaches the tissue through the hypophyseal portal circulation and may thus have a role in the regulation of pituitary function.

It is not surprising that hypothalamic neuroendocrine transducer cells receive neuronal afferents that release monoamines and ACh or that they release hormones in the pituitary in response to these stimuli. It is interesting however, that the rates at which neurons synthesize 5-hydroxytryptamine, catecholamines and ACh depend in part on the

availability of their circulating precursors, tryptophan, tyrosine and choline, respectively. These are naturally occurring dietary constituents that are transported into the brain from the systemic circulation (Growdon and Wurtman, 1978).

2. Effects of Hormones on Cholinergic Neurochemistry

Glucocorticoids, insulin and thyroxine exert significant influences on cholinergic metabolic processes. Effects on the cholinergic system are generally opposite to the effects on catecholaminergic neurons. Those hormones that subserve opposing metabolic functions often exert opposing effects on a given transmitter system. Specifically, glucocorticoids stimulate catecholamine biosynthesis, elevate tyrosine hydroxylase-specific activity, but depress ACh synthesis and storage in a clone of sympathetic nerve-like cells. Insulin opposes the action of glucocorticoids on ACh synthesis by raising choline acetyltransferase-specific activity (Schubert et al, 1980). This effect of insulin has been confirmed in vitro in preparations from cortex and striatum but not in vivo. Thyroxine accelerates ACh synthesis in cortex in vivo without changing absolute concentrations of ACh. This effect does not occur in vitro (Billewicz-Stankiewicz et al, 1980).

Considerable attention has been given to the possible roles of the cholinergic septo-hippocampal pathway and its projections to hypothalamic nuclei involved in parasympathetic outflow and the vomiting reflex (Section E). Because septal lesions potentiate both behavioral and hormonal responses to stress, as measured by plasma levels of corticosterone, growth hormone and prolactin (Seggie and Uhler, 1979), it follows that this pathway may also be involved in stress and release of hormones from the anterior pituitary. Further evidence for this role is obtained from the discovery of ACTH receptors in the septum. Stimulation of these receptors inhibits release of ACh in the hippocampus (Botticelli and Wurtman, 1981).

H. SUGGESTIVE DATA FROM SKYLAB

Nine astronauts participated in the three Skylab missions; five of them demonstrated signs of motion sickness. Hematological studies revealed that those astronauts who had echinocyte levels greater than 1% of the red blood cell population on either the day before flight or on mission day 3 or 4 experienced motion sickness symptoms. This correlation prevailed despite the use of anti-motion sickness drugs. Lecithin, lysolecithin, and free fatty acids are known echinocytogenic agents. Unfortunately, the levels of these factors were not measured during the Skylab missions (Kimzey, 1977). The presence of elevated plasma lecithin and lysolecithin might facilitate the formation of ACh and enhance cholinergic function as described earlier. This effect could be antagonistic to the anti-motion sickness effects of scopolamine. Consequently, altered susceptibility to motion sickness may have resulted, at least in part, by this mechanism.

Another interesting observation derived from data collected during the Skylab missions concerns the levels of acetylcholinesterase in red blood cells. In all cases there was a pronounced decrease in

acetylcholinesterase levels following launch. This decrease was greater during the Skylab 3 and 4 missions. The absolute levels also were lower during these missions in comparison to Skylab 2 (Mengel, 1977). These reductions in the levels of acetylcholinesterase might significantly inhibit ACh metabolism in the circulatory system and possibly in the central nervous system as well. The astronauts of Skylab 2, as mentioned above, did not show any signs of motion sickness. It is entirely possible that circulatory levels of acetylcholinesterase play a role in determining an individual's susceptibility to sickness induced by stressful motion or a zero-gravity environment.

The neurochemical and neuropharmacological control of pituitary hormones has been discussed already (see section G). Eversmann, et al (1978) have reported that the stress of motion sickness in man leads to increased secretion of growth hormone, cortisol, prolactin and ADH. Aerobatic flight (30 minutes) elevates the serum levels of growth hormone, prolactin and free fatty acids in untrained personnel but not in trained pilots. All of the novices experienced dizziness and mild, brief bouts of nausea. When either group was subjected to caloric stimulation of the labyrinth, dizziness, nausea, and nystagmus followed but no hormonal changes were demonstrable (Pinter et al, 1979). When experienced pilots are subjected to more strenuous flight, a late increment occurs in both growth hormone and free fatty acid levels (Pinter, 1974). It is not clear why caloric irrigation does not elicit any hormonal changes. Further studies are needed to clarify the situation.

Data from the Skylab missions has revealed a 50% rise in growth hormone in plasma 3-4 days after launch. The magnitude of this rise is in line with results obtained by Pinter (1974). The levels of excretion of urinary ADH immediately following launch did not match the results of Eversmann et al (1978), however. Levels of ADH were actually diminished following launch with the exception of those measurements obtained from Skylab-2 (Leach and Rambaut, 1977). Presumably, the shift in fluid towards the head that occurs during zero-gravity exerts a stronger influence on ADH release. The incongruity of the findings early in the Skylab-2 mission is most likely explained by the unusually heavy load of work these astronauts had in erecting a heat shield outside of the vehicle and by the high environmental temperatures that prevailed.

Secretion of cortisol is decreased by intrahypothalamic administration of anticholinergic agents (Endroczi et al, 1963; Krieger et al, 1968; Cozanitis 1974; Hillhouse et al, 1975). Significant elevations of both the levels of urinary and plasma cortisol occurred inflight and post-flight. Anti-motion sickness drugs such as scopolamine were taken by the crew of Skylab-3 and 4, but were generally ineffective in preventing the rise in cortisol. The crew of Skylab-2 received little or no medication and yet maintained the lowest levels of urinary cortisol. There appears to be no relationship between the changes in the levels of cortisol and the administration of scopolamine. Members of Skylab-3, for example, demonstrated a rise in urinary cortisol in advance of any anti-motion sickness medication. It is interesting, however, that those two crewmen who actually vomited during the Skylab missions had the highest levels of secretion of cortisol. Levels of urinary cortisol in these crewmen were elevated in excess of 180% by the first day of flight, whereas, levels in

members of Skylab-2 ranged from 0-40% higher. Levels of circulating ACTH were significantly decreased by the third to fourth day inflight (Leach and Rambaut, 1977). Urinary excretion of cortisol was not increased significantly in studies on the ground by stressful head movements in the rotating chair (Eversmann et al, 1978).

I. SUMMARY AND CONCLUSIONS

The problems and nature of space motion sickness have been defined. The neurochemical and neurophysiological bases of vestibular system function and of the expression of motion sickness have been reviewed. Considerable emphasis was given to the elucidation of the neuropharmacological mechanisms underlying the effects of scopolamine and amphetamine on motion sickness. Characterization of the ascending reticular activating system and the limbic system has provided clues into the etiology of the side effects of scopolamine, but more importantly, it has given us insight into the operation and functional activity of the central cholinergic nervous system. The interrelationship between central cholinergic pathways and the peripheral (autonomic) expression of motion sickness was described. A correlation between the stress of excessive motion and a variety of hormonal responses to that stress was also detailed.

The cholinergic system is the common denominator in most of the experimental work described above. It is involved in the efferent modulation of the vestibular hair cells, as an afferent modulator of the vestibular nuclei, and in the activation of cortical and limbic structures. ACh also is involved in the expression of motion sickness symptoms and most likely underscores a number of the hormonal changes that occur in stressful motion environments. Because of the extensive involvement of ACh throughout these motion related systems, it is reasonable to expect that a potent anticholinergic drug such as scopolamine would exert a significant modulatory role in the expression of motion sickness.

It is both reasonable and likely that the dietary administration of pharmacological doses of lecithin would exert a definite modulatory role in the expression of motion sickness as well. The effects of lecithin and choline on the absolute and functional levels of ACh in brain supports this role. Emphasis has been given to the accepted use and benefit of such an approach in the treatment of several disorders that involve abnormal cholinergic neurochemistry (see also Section III). This so-called precursor-load strategy is not a new approach and is not restricted to just the cholinergic system. The pharmacological manipulation of the cholinergic system by the administration of lecithin or choline is in large part dependent on the concept that the function of the central nervous system is responsive to the nutritional state of the organism. It is the opinion of the author that this concept is both experimentally founded and intuitively practical.

The foundation for future experimentation on motion sickness has been laid in the course of the above presentation. Specifically, future experimentation might include investigation of the effects of drugs that modify high affinity choline uptake. Experiments with choline and lecithin would provide support for the development and testing of new

choline drugs. The advantage to initial experimentation with lecithin is that it comprises use of a safe, normal dietary component that has been administered for years.

III. PHARMACODYNAMICS AND SIDE EFFECTS OF LECITHIN AND CHOLINE ADMINISTRATION

A. Experimental Plan of Research in Progress at Johnson Space Center

Subjects participating in the experiment will consume 25 grams of soy lecithin (90% phosphatidylcholine) per day in 1-2 divided doses. Diets will be supplemented with lecithin for 3 weeks at which time the final experimental test with the staircase velocity motion stressor will be performed.

B. Background

Both choline and lecithin supplements have been given to human subjects for the experimental treatment of various disease states believed to involve deficient cholinergic activity. This approach has resulted in clinical improvement in the symptoms of tardive dyskinesia and Huntington's Chorea (Growdon *et al*, 1977, 1978; Gelenberg *et al*, 1979; Davis, 1979), with little or slight benefit to those individuals suffering from Friedreich's Ataxia, Gilles de la tourette's disease and Alzheimer's disease (Barbeau, 1978).

Earlier experimentation employed choline almost exclusively to effect a rise in serum choline levels. Normal plasma levels of choline are $11.2 \pm 0.7 \mu\text{M}$ ($n=19$) for normal individuals (Chamberlain *et al*, 1980). Typically used doses of choline or lecithin significantly raise plasma choline to levels in the 23-36 μM range (Growdon *et al*, 1977, 1978; Chamberlain *et al*, 1980). Figure 3 best describes the differences in the response of plasma choline to ingested choline versus ingested lecithin. Lecithin doses that actually contain less molecular choline than the choline supplement elevate the levels of choline in plasma for a considerably longer period of time than choline alone (Ziesel *et al*, 1980 a,b).

C. Side Effects Following Choline and Lecithin Administration

Interpretation of the incidence and nature of the side effects following choline and lecithin administration is complicated by each investigator's selection of different treatment regimens. Generally, the longer a lecithin or choline preparation is given or the higher the dose that is given, the greater the incidence of side effects. The purity of the lecithin used; that is, the percentage of phosphatidylcholine that preparation contains, will be a major factor in determining the amount of lecithin given. Depending on the supplier, phosphatidylcholine content ranges from 20 to 90%.

Earlier clinical studies employed choline almost exclusively. Doses of 150 - 200 mg/kg/da (approximately 14 g/da) for 2 weeks (Growdon *et al*, 1977) were typical. Side effects frequently encountered included diarrhea, an unpleasant "fishy" body odor (probably reflecting the trimethylamine formed from choline by intestinal bacteria) and a bitter taste (Zeisel *et al*, 1980a).

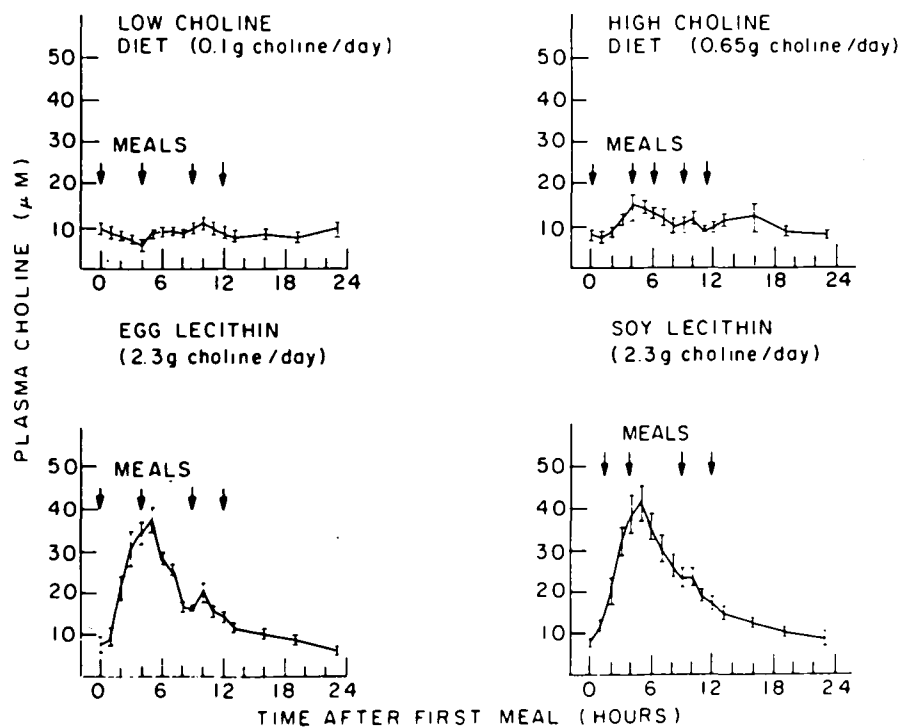


Figure 3. Plasma choline response to ingested choline and lecithin. Six adult human subjects ingested each of four diets (common foods high in choline, common foods low in choline diet plus breakfast supplement of 25 gm 80% pure egg lecithin and low-choline diet plus breakfast supplement of 25 gm 80% pure soy lecithin). Plasma samples were obtained at regular intervals and assayed for choline. Meal times are indicated by arrows. Data are expressed as mean \pm SD. (By permission).

Most of the reports describing experimental feeding of lecithin do not indicate whether or not side effects were experienced. One should not assume that there were no side effects in these studies but might conclude that the likelihood of there being any major side effects was minimal. Zeisel *et al* (1980a) have reported that lecithin has fewer side effects than choline and does not possess a bitter taste. Minimal side effects were encountered such as indigestion, weight gain and minor diarrhea, with no consistent mental changes or alterations of hematological or hepatic indices. These observations were derived from an experimental protocol that required the administration of 60-80 grams of lecithin (20% phosphatidylcholine) for 6 weeks. Another study which employed 50-100 grams of lecithin per day for 8-16 weeks also reported side effects of diarrhea, nausea, depression, "hot flashes" and weakness, but only in the patients who suffered from ataxia and who consumed the 100 gram dose (Chamberlain *et al*, 1980). These doses and administration periods are all higher than the doses and administration periods employed by other investigators who make no mention of side effects: 25 g/da x 2 weeks (Branchey *et al*, 1979), 24 g/da x 8 weeks (Barbeau, 1978), and 25 g/da x 1 day (Ziesel *et al*, 1980b). Additional studies have indicated that the source of lecithin does

not affect its ability to raise choline levels in brain. Soybean and egg lecithins differ in terms of fatty acid composition; the former containing 72% polyunsaturates vs 20% (see figure). (Zeisel et al, 1980b; Magil et al, 1981). It is not known if the fatty acid composition influences side effects. Experiments at Johnson Space Center will employ polyunsaturated soybean lecithin in accordance with current clinical and nutritional preference. Based on these findings, a daily dose of 25 grams of soy lecithin (90% phosphatidylcholine) for 3 weeks was considered to possess minimal side effects if any. Selection of this dosage level was based on pharmacodynamic studies as well (Section B).

D. Methods of Preparation of Lecithin for Daily Consumption

Although there have been reports that some individuals enjoy the taste of plain lecithin, most people prefer to disguise the taste by incorporating the lecithin into other preparations. Three preparations have been described and are detailed below:

Preparation (No. 1)

Ingredients:

Lecithin (daily dose up to 100g)
1/2 cup water
3 1/2 teaspoons polycose (or other sugar)
1 cup milk
1/2 cup vanilla ice cream
2 teaspoons instant coffee

Preparation:

1. Mix lecithin and water in a blender (chop setting)
2. Dissolve till a pudding consistency, then add milk, sugar and coffee
3. Mix thoroughly, then add ice cream blend

Enough to make 3-4 six-ounce drinks

Formulate by Maureen Quirk, R.D.
(From: Ziesel et al, 1980a)

Preparation (No.2)

Up to 25 grams of lecithin as an emulsion
in hot coffee and sugar

(From: Branchey et al, 1979)

Preparation (No.3)

25 grams of lecithin mixed with Kool-Aid
and taken in three divided doses.

(From: Growdon et al, 1977)

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1. Report No. NASA CR-3569		2. Government Accession No.		3. Recipient's Catalog No.	
4. Title and Subtitle Neurochemical Background and Approaches in the Understanding of Motion Sickness				5. Report Date July 1982	
				6. Performing Organization Code	
7. Author(s) Randall Lee Kohl				8. Performing Organization Report No. S-515	
9. Performing Organization Name and Address Technology Incorporated Life Sciences Division 17625 El Camino Real, Suite 311 Houston, Texas 77058				10. Work Unit No. 199-99-00-00-72	
				11. Contract or Grant No. NAS 9-14880	
12. Sponsoring Agency Name and Address National Aeronautics and Space Administration Washington, D.C. 20546				13. Type of Report and Period Covered Contractor Report	
				14. Sponsoring Agency Code	
15. Supplementary Notes Prepared for Lyndon B. Johnson Space Center, Neuroscience Research Laboratory. Jerry L. Homick, Technical Monitor					
16. Abstract The problems and nature of space motion sickness have been defined. The neurochemical and neurophysiological bases of vestibular system function and of the expression of motion sickness have been reviewed. Considerable emphasis was given to the elucidation of the neuropharmacological mechanisms underlying the effects of scopolamine and amphetamine on motion sickness. Characterization of the ascending reticular activating system and the limbic system has provided clues in to the etiology of the side effects of scopolamine. The interrelationship between central cholinergic pathways and the peripheral (autonomic) expression of motion sickness was described. A correlation between the stress of excessive motion and a variety of hormonal responses to that stress was also detailed. The cholinergic system is involved in the efferent modulation of the vestibular hair cells, as an afferent modulator of the vestibular nuclei, in the activation of cortical and limbic structures, in the expression of motion sickness symptoms and most likely underscores a number of the hormonal changes that occur in stressful motion environments. The role of lecithin in the regulation of the levels of neurotransmitters was characterized as a possible means by which cholinergic neurochemistry can be modulated. The pharmacological manipulation of the cholinergic system by the administration of lecithin or choline is in large part dependent on the concept that the function of the central nervous system is responsive to the nutritional state of the organism. The effects of lecithin and choline on the absolute and functional levels of ACh in brain supported this concept. Emphasis has been given to the accepted use and benefit of lecithin in the treatment of disorders involving abnormal cholinergic neurochemistry. A brief discussion of the pharmacodynamics and side effects of lecithin administration in man was presented. Summarizing, sufficient information was provided to design and justify experimental research on the central cholinergic system in man with respect to the problems of motion sickness.					
17. Key Words (Suggested by Author(s)) acetylcholine, amphetamine, choline, hormones, lecithin, motion sickness, neurochemistry, neurophysiology, scopolamine, Shuttle, Skylab				18. Distribution Statement Unclassified-Unlimited Subject Category: 52	
19. Security Classif. (of this report) Unclassified		20. Security Classif. (of this page) Unclassified		21. No. of Pages 53	
				22. Price* A04	

End of Document